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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/606,222	06/29/00	THOMAS K	2323-139-II

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/606,222	Applicant(s) THOMAS ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- Th MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *18 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-17, 19-35 and 37 drawn to methods for detecting a nucleic acid sequence in specified tissues of an animal, a nucleic acid molecule, and a transgenic animal containing the nucleic acid molecule, classified in class 435, subclass 6, class 800, subclasses 3, 8, and 13, class 536, subclass 23.1, for example .

II. Claims 1-16, 18 and 20-36, drawn to methods for detecting a nucleic acid sequence in the specified tissues of a plant, a nucleic acid molecule and a transgenic plant containing the nucleic acid molecule, classified in class 435, subclass 6, class 536, subclass 23.1, class 800, subclass 278, for example.

The inventions are distinct, each from the other because of the following reasons:

Invention I is patentably distinct from Invention II in that the transgenic animal and the methods of using the transgenic animal in Invention I require different technical considerations than the transgenic plant and the methods of using the transgenic plant in Invention II. The differences between Inventions I and II are further underscored by their independent search status.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Jeffrey Ihnan on June 7, 2001, a provisional election was made with traverse to prosecute the invention of Group 1,

claims 1-17, 19-35 and 37. Affirmation of this election must be made by applicant in replying to this Office action. Claims 18 and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-17, 19-35 and 37 are pending and being examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 19-35 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for deleting a nucleic acid sequence in a specified tissue of a mouse from a DNA molecule introduced into the mouse, comprising introducing a DNA molecule which comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, growing the mouse so that the tissue-specific promoter is active for expression of the

recombinase gene in the specific tissue, and where the foreign DNA is deleted in the specified tissue during growth of the mouse, the specification does not reasonably provide enablement for a method for deleting a nucleic acid sequence in a specified tissue of all organisms from a DNA introduced into the organism, comprising introducing a DNA molecule which comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, the growing of all organisms so that the tissue-specific promoter is active for expression of the recombinase gene in the specific tissue, and where the foreign DNA is deleted in the specified tissue during growth of all organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a method for deleting a nucleic acid sequence in a specified tissue of an organism from a DNA molecule introduced into the organism comprising introducing a DNA molecule into the organism, where the DNA molecule comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA molecule and a recombinase site, growing the organism so that the tissue-specific promoter is active for expression of the recombinase gene in the specified tissue, where the foreign DNA is deleted in the specified tissue during the growth of the organism. The invention is further directed to the use of the above-stated method for gene therapy or in the production of a transgenic organism.

The specification teaches a method of self-excision of nucleic acid sequences in specific tissues of organisms by use of a DNA molecule comprising a recombinase site,

a tissue specific promoter, a recombinase gene, a foreign DNA and a recombinase site. The specification teaches that the tissue specific promoter can be a gamete or somatic tissue specific promoter. The specification teaches that the method of the invention can be used to produce a transgenic organism containing the DNA molecule (see p. 2, lines 24-25) or used introduced into an organism for gene therapy (see p. 4, lines 12—13 and 30-31, for example). The specification further teaches that the foreign DNA can be heterologous DNA, such as a marker sequence, or a wild-type allele used for gene therapy which is desired in the germline of the transgenic organism (see p. 4, last paragraph) The specification teaches that recombinase sites in the DNA molecule, such as *loxP* and *FRT*, and recombinase genes such as *Cre* and *FLP* can be used (see p. 5, 3rd paragraph). The specification specifically teaches self-induced deletion of nucleic acid sequences in the germline of male mice using a cassette (referred to as ACN) containing the murine angiotensin converting enzyme promoter (tACE) to drive expression of two genes, *Cre* and the selectable marker gene, *Neo*^{r}, where the two genes are flanked by *loxP* sites (see p. 5, 3rd paragraph). The specification specifically teaches that to generate the targeting vector, ACN was assembled into a bacterial plasmid. Murine *Hoxa3* sequences were isolated from λ phage library and ACN was inserted in exon 2 (see Example 1). The targeting vector was then introduced into RI ES cells and clones that were heterozygous at the *Hoxa3* locus were injected into blastocytes and allowed to come to term. The chimeric mice were then identified and mated with C57B1/6 females (see Example 2). DNA was then extracted and analyzed from the chimeric mice and their progeny (see Example 3).

It appears the elements essential to the claimed invention are embryonic stem cells (see p. 5, last paragraph, and Example 2). However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, S*ummary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

> "The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of <u>any</u> species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal.

In addition, prior to the time of filing, Mullins *et al.* (**Journal of Clinical Investigation**, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the

generation of a transgenic animal, the state of the art supports that only **mouse ES cells** were available for use for production of transgenic mice.

With particular regard to the claims directed to the use of the above-described construct in germline gene therapy, it is well known that the status of the gene therapy art, and in particular, the germline gene therapy art, is undeveloped and unpredictable in terms of achieving *in vivo* therapeutic expression levels of a gene of interest. See **Gene Therapy, A Handbook for Physicians**, Introduction, page xii, wherein Culver reports that only somatic cell gene therapy is technically feasible and ethically acceptable for human use, and that germline gene therapy, which is practiced in animals, can eliminate a disease for all generations, but at this time is neither technically feasible nor ethically resolved. Culver goes on to report that the RAC (Recombinant DNA Advisory Committee) of NIH will not consider any germ-line gene therapy protocols, and that the technology for human germ-line manipulation is too inefficient and too preliminary in its development for consideration. See page 79.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving a method for deleting a nucleic acid sequence in the specified tissue of an organism, the lack of guidance and direction in the specification for the isolation of animal ES cells from species other than mouse, the unpredictable and undeveloped state of the art for the isolation of animal ES cells from species other than mice, wherein the cells contribute to germline tissue and the whole organism, as well as the claimed breadth encompassing use of all species of ES cells for the generation of all species of organisms, and the lack of guidance and direction in

the specification to carry out gene therapy as broadly claimed involving any target cells, routes of administration, and subjects, the absence of working examples for the demonstration or correlation to achieving any therapeutic gene expression *in vivo*, and in particular, the unpredictable and undeveloped art of germline gene therapy, the specification fails to enable the claimed invention and it would have required undue experimentation for one skilled in the art to carry out the claimed methods, nucleic acid constructs and uses thereof.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 14, 22-24, and 27-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 14 recite the limitation "the introduction" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 22 and 23 recite the limitation "said recombinase gene" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim 24, and 27-34 recite the limitation "the method" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 and 27-34 are drawn to methods, but no clear and defined steps are recited in the independent claims. While minute details are not required in method

claims, at least the basic steps must be recited in a positive, active fashion. See Ex Parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986).

Conclusion

Claims 1-17, 19-35 and 37 appear to be free of the prior art of record, as the prior art of record fails to teach or suggest a method for deleting a nucleic acid sequence in a specified tissue of an animal from a DNA molecule introduced into the animal, where the DNA molecule comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, and growing the animal so that the tissue-specific promoter is active for expression of the recombinase gene and the foreign DNA is deleted in the specified tissue during growth of the animal, DNA molecules of the same, and transgenic non-human animals comprising the DNA molecules of the same. However claims 1-17, 19-35 and 37 are subject to other rejections.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

TNT

Thaian N. Ton
Patent Examiner
Group 1632

JILL D. MARTIN
PRIMARY EXAMINER